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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,575	08/04/2005	Salah-Dine Chibout	DC4-32567A	7721

1095 7590 12/18/2007

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
POHNERT, STEVEN C	
ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
12/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,575	CHIBOUT ET AL.	
	Examiner	Art Unit	
	Steven C. Pohnert	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) *3,4,12,15,21,22,29,30 and 37-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-11,13,14,16-19,23-28 and 31-37* is/are rejected.

7)☒ Claim(s) *6-8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *22 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/14/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Sequence Compliance

1. The application fails to comply with CFR 1.821(d), which states:

> (d)Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

For example, Table 2, contains a nucleic acid sequence. Applicant is required to check the rest of the disclosure for any other nucleic acid or protein sequences and list them in a sequence listing and identify them with a proper SEQ ID NO.

The specification must be amended to bring it into sequence compliance. **A response to this office action will be held non-compliant if the specification has not been amended to make it sequence compliant.**

Election/Restrictions

2. Applicant's election without traverse of group I, claims 1-11 and 13-36 and the combination of KIM-1 and clusterin, in the reply filed on 9/26/2007 is acknowledged.

3. Claims 12, 37-60 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 9/26/2007.

Further claims 3, 4, 15, 21, 22, 29, 30 are withdrawn from consideration as they do not require the elected combination of KIM-1 and clusterin.

Information Disclosure Statement

4. The references have been reviewed. It is noted that the IDS contained an error and WO09/37757 is properly identified as WO99/37757.

Claim Objections

5. Claims 1–2, 5-11, 13-14,16-20, 23-28, 31-36 are objected to because of the following informalities:

Claims 1-2, 5, 9, 10 and 11 recite, "first 10 value lower". This is grammatically incorrect. Appropriate correction is required.

6. Claims 6-8 are objected to because of the following informalities:

Claims 6-8 recite, "clusterin alpha-2u". This is believed to be a typographical error and is being interpreted as "clusterin, alpha-2u." Appropriate correction is required.

7. Claims 1–2, 5-11, 13-14,16-20, 23-28, 31-36 are objected to because they specifically recite nonelected subject matter. The claims require "Alpha-2u globulin related-protein (Alpha-2u), Complement component 4 (C4), Vascular Endothelial Growth Factor (VEGF), Kidney-specific Organic Anion Transporter-K1 (OAT-K1), Aldolase A, Aldolase B and Podocin." As stated in the response to the restriction filed 9/26/2007, applicant has elected a clusterin and KIM-1. Applicant should amend the claims so that the claims are directed to the elected invention of the specific combination of genes.

Prior to allowance of these claims, the non-elected subject matter will be required to be deleted from the claims

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1–2, 5-11, 13-14,16-19, 23-28, 31-36 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors have been described by the court in re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in the Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

<u>The nature of the invention and the breadth of the claims:</u>

The claims are broadly drawn to a method of determining renal toxicity in "any" individual by obtaining a bodily sample, determining gene expression of KIM-1 and clusterin to determine a first set value, comparing the first set value with a second value from an individual not subject to renal toxicity wherein the first value being greater than the second value for KIM-1 and clusterin, indicating the individual is having developing or is sensitive to renal toxicity.

The claims thus are broadly drawn to the "any" individual which include dog, cats, apes, rats, etc.

The claims are broadly drawn to analysis of gene expression in "any" bodily sample.

Further the claims are drawn to "any" gene in any species that can broadly be encompassed by the recitation of KIM-1 or clusterin. This includes any cDNA, splice variant, SNP, mutant, etc.

The claims further encompass any level of increased expression of clusterin and KIM-1 in the first sample relative to the second sample from .0001% increase on up.

Further the claims do not set forth how or if the samples are to be normalized so the expression data comprise raw as well as normalized data.

The claims are thus broadly drawn to detection of mRNA, protein, or activity levels.

Further the claims are drawn to "any" type of renal toxicity caused by any compound.

Later claims further limits the compound to cytotoxic agents: cyclosporine, cisplatin, tacrolimus, aminoglycosides, sulfonamides, trimethadone.

Dependent claims draws the absolute mRNA expression level to KIM-1 to above 1.5 E+07 and clusterin above 1.90E+09 or a 20 fold overexpression of Kim 1 and at lest a 7 fold overexpression of clusterin.

The claims are broadly drawn to a method of modulating renal toxicity of an individual by treatment with an effective amount of a modulating compound that modulates kidney synthesis, expression or activity of KIM-1 or clusterin. This broadly encompasses gene therapy, antisense molecules, small molecules, ligands, antibodies and antagonists.

The claims are further drawn to identifying candidate compounds for treatment of renal toxicity by treating kidney tissue with a candidate agent and examining expression levels of KIM-1 and clusterin.

The claims are further drawn to identifying candidate compounds that do not induce renal toxicity by treating kidney tissue with a candidate agent and examining expression levels of KIM-1 and clusterin.

The amount of direction or guidance and the Presence and absence of working examples.

The specification teaches in Table 1 sequences for KIM-1 are available by Genbank accession AF035963, AL159977, AC073225.5, AC025449.6, AF165926, AL449103, AI662116.

The specification teaches in Table 1 sequences for clusterin are available by Genbank accession U02391, M64723, M64723, J02908, L00974, M25915, M63379, M64722, M74816, X14723, AF182509, D14077, L05670, L08235, S70244.

The specification teaches in experiment 1 treatment of rats with cyclosporin A and isolation of RNA from the kidneys and analysis by probe arrays (see page 35). The specification does not teach which array was used and thus does not teach which genes were present on the array to normalize expression between samples.

The specification further teaches that serum clusterin levels were increased in animals treated with nephrotoxic compounds (see table 3). However, the specification does not teach this increase is statistically significant.

The specification further teaches that real time PCR analysis demonstrated that as pathology grade of kidney failure increased so did the expression of clusterin and Kim-1 relative to B-actin levels(see figure 1).

The specification further teaches in experiment 2, a study of rats treated with test compound 1 (TC1) in cyclosporine A at 20 mg/kg/day, 60 mg/kg/day for 14 days , or in cyclosporine A at 10 mg/kg/day, 25 mg/kg/day for 25 days a control microemulsion (see page 37, lines 17-25). The specification teaches these genes were analyzed by PCR and the data is represented in Figure 3. Figure 3 appears to suggest that TC1 was administered alone with the emulsion. Figure 3 further teaches that the TC1 resulted in between a 1 and 10 fold increase Kim-1 expression in male and female rats at doses examined. However, TC-1 resulted in decreased expression of clusterin in males rats at all doses and with a at females at 60 mg/kg/day. Further figure 3 teaches that 20

mg/kg of cyclosporine A increases KIM-1 expression approximately 90 fold, and clusterin expression approximately 3 fold. The specification asserts on page 38 that this data confirms the validity of prediction based on these marker genes. The specification does not present any data as to the kidney status of any groups; so that one could form a nexus that increased KIM-1 and clusterin expression are correlated with renal toxicity.

The specification teaches experiment 4 in which male rats were treated with 5 or 20 mg/kg/day of cyclosporine A and compared to controls (see page 39, lines 5-10). The specification does not teach if the controls were treated with the cyclosporine A carrier, or not treated at all. The specification further teaches RNA was isolated from kidneys and analyzed by Affymetrix RU34A rat gene chips (see page 39, line 20). The specification teaches, "For the genes listed in Table 6, the overall differences among the different treatment groups were statistically significant ($p<0.001$)" see page 39, lines 25-26). The specification teaches in Table 6 that KIM-1 expression has a control value of 6.5 in 16 control rats, 5.9 in 4 rats treated with 5 mg/kg/day of cyclosporine A, and 168 in 7 rats treated with 20 mg/kg/day of cyclosporine A. The specification teaches in Table 6 that clusterin expression has a control value of 305 in 16 control rats, 302 in 4 rats treated with 5 mg/kg/day of cyclosporine A, and 2309 in 7 rats treated with 20 mg/kg/day of cyclosporine A. It is unclear how there is a statistical difference in the expression of KIM-1 and clusterin between the low dose and controlgroups as suggested by the teachings of the specification.

The specification appears to contradict the teachings of page 39, lines 25-26 on page 41 where it states, " As shown in Table 6, the expression of KIM-1 was induced

26-fold in rats treated with 20 mg/kg/day CsA as compared to the control rats ($p<0.001$). No induction of KIM-1 was detected in rats treated with 5 mg/kg/day CsA. The changes in KIM-1 expression by CsA (20 mg) compared to CsA (5 mg) are statistically significant ($p<0.004$)."

The specification appears to contradict the teachings of page 39, lines 25-26 on page 41 where it states, " The expression of Clusterin was induced 7.6-fold in rats treated with 20 mg/kg/day CsA as compared to the control rats (Table 6; $p<0.001$). No induction of Clusterin was detected in rats treated with 5 mg/kg/day CsA. The changes in Clusterin expression by CsA (5 mg) compared to CsA (20 mg) are statistically significant ($p<0.001$)."

However, the data of experiments 2 and 4 demonstrate great variability in the effect of 20 mg/kg/ day cyclosporine A on clusterin and KIM-1 expression, suggesting the fold increase in expression of these gene is not predictable. Further as experiment 2 clearly demonstrates that female and male rats respond differently to the same compounds it would be unpredictable to correlate findings in males with female rats.

Presence and absence of working examples

The specification does not teach any a method of detecting absolute levels of mRNA.

The specification does not teach cyclosporine, cisplatin, tacrolimus, aminoglycosides, sulfonamides and trimethadione have a similar mode of action. Further the specification does not teach how these drugs cause renal toxicity, such that a nexus between the teachings of cyclosporine can be extrapolated in any other drug.

The specification does not teach an activity of KIM-1 or clusterin and thus does not teach a method of assaying their activity.

The specification does not teach a study demonstrating that Kim-1 or clusterin protein levels are markers for renal toxicity or are correlated with mRNA expression levels.

The specification does not set forth any teachings as to specific modulating compounds, antisense RNA, small drugs, ligands, antibodies or antagonists.

The state of prior art and the predictability or unpredictability of the art:

KIM-1 Genecard (HAVCR GC05M156389, 11/27/2007, pages 1-9) teaches there are 23 cDNAs and 168 SNPs of the Kim-1 gene.

The Clusterin gene card (CLU GCM08M027510, 11/27/2007) teaches there are 3200 known cDNAs and 151 known SNPs of the clusterin gene.

Vandesompele teaches, "Accurate normalization of gene expression levels is an absolute prerequisite for reliable results, especially when the biological significance of subtle gene expression differences is studied" (see page 9, 2nd column, discussion) (Vandesompele et al (Genome Biology (2002) volume 3 , pages 1-11). Vandesompele teaches, "That the conventional use of a single gene normalization leads to relatively large errors in a significant portion of samples tested" (see abstract, results). Vandesompele teaches that ACTB (beta actin) appears to be the one of the worst genes fro normalization and thus resulting in large normalization errors (see page 10, 1st paragraph). Vandesompele teaches at least 3 housekeeping genes are required for

accurate normalization (see page 10, 1st column, 1st full paragraph). Vandesompele thus teaches that studies of gene expression using a single gene for normalization are unpredictable due to the large variation in the expression of the genes used for normalization.

The art of Cheung et al (Nature Genetics, 2003, volume 33, pages 422-425) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) p.422, last paragraph; Fig 1). The data indicates that, for example, expression of ACTG2 in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3).

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the prior art of Wu (Journal of Pathology, 2001, volume 195, pages 53-65). Wu teaches that gene expression data must be interpreted in the context of other biological knowledge, involving various types of 'post genomics' informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (p.63 - Discussion). The prior

art of Newton et al (Journal of Computational Biology, 2001, volume 8, pages 37-52) further teaches the difficulty in applying gene expression results. Newton et al teaches that a basic statistical problem is determining when the measured differential expression is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation (p.38, third full paragraph).

Greenbaum et al (Genome Biology 2003, volume 4, article 117, pages 1-8) teaches that protein and mRNA levels are not predictably correlated (see abstract). Greenbaum teaches the same mRNA expression levels can be accompanied by upto 20 fold differences in protein levels (page 4, 1st column, 1st full paragraph). Greenbaum et al further teaches there are 3 reasons for a lack of correlation between mRNA and protein levels. First there is post-transcriptional regulation of protein synthesis. Second, proteins have different half-lives than mRNA. Third, there is a significant amount of error in the determination of protein and mRNA levels (see page 4, 2nd column, 1st full paragraph).

Perazella et al (Expert Opinion on Drug Safety, 2005, Volume 4, pages 689-706) teaches the mechanism of drug toxicity can vary greatly with pharmacological action, metabolism and ultimate pathway of excretion of agen administered (see page 689, 1st paragraph after abstract). Perazella et al teaches that cyclosporine and tacrolimus are associated with prerenal azotemia, renal vascular disease, but not glomuler disease, interstitial nephritis, acute tubular necrosis, crystal nephropathy, or post-renal azotemia (see boxes 1-8). Perazella further teaches the cisplatin is associated with vascular kidney disease, interstitial nephritis, acute tubular necrosis, crystal nephropathy,

postrenal azotemia (see boxes 1-8). Perazella further teaches the aminogylcosides are associated with acute tubular necrosis (see boxes 1-8). Thus Perazella teaches the recited cytotoxic drugs have different modes of action and affect the kidney differently. Due to Perazella's teachings it would be unpredictable to associate the different drugs recited with the same renal toxicity as each has a different with pharmacological action, metabolism and ultimate pathway of excretion of agent administered.

Robinson et al (PLoS biology (2004) volume 2 page 0018-0020) teaches, " but for all its promise RNAi therapy is a long way from entering the clinic. While it is proven in the lab, to date no test have been done on humans" (see page 0018, 1st column, last full paragraph). Robinson further teaches that stability and delivery are major issues with RNAi (see page 0019, 2nd column, lat paragraph).

Bennett (Antisense &Nucleic Acid drug development (2002) volume 12, pages 215-224) teaches less than 2% of all new drug projects have a chance to succeed.

While progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to desired sites has continued to be unpredictable and inefficient for the past decade. This statement is supported by numerous teachings available in the art. For example, **Pouton** et al. (Pouton and Seymour, Key issues in non-viral gene delivery, *Adv Drug Deliv Rev.* 46(1-3): 187-203, 2001) reviewed the issues in non-viral gene delivery and stated that, "direct injection of gene medicines into target tissue represents a far simpler task than targeting delivery to a specific tissue from the systemic circulation". See last full sentence on page 188, right column, and section 2.1. Pouton et al. added that there were "no systems yet available for efficient tissue

targeting following systemic delivery." (See page 189, first sentence of section 2.2.). **Kumar** et al. reviewed chitosan-related nanoparticle-mediated gene delivery stated that, nanoparticles have been pragmatically divided as chitosan-related and chitosan-unrelated nanomaterials. The state of the art in terms of the development, characterization and evaluation of their in vitro and/or in vivo potential is discussed for each of these various particles. Although substantial progress has been made, the potential of these particles in the clinical arena and human responses remain to be evaluated. (Kumar et al. Nanoparticle-mediated gene delivery: state of the art. *Expert Opin Biol Ther.* 4(8): 1213-24, 2004).

The level of skill in the art:

The level of skill in the art is deemed to be high.

Quantity of experimentation necessary:

In order to practice the invention as claimed the skilled artisan would first have to determine which is broadly encompassed by the recitation of KIm-1 and clusterin and in which species these genes are correlated with renal toxicity. This would be unpredictable in that Genecard teaches that Kim-1 is at least 23 cDNAs and 168 SNPs of the Kim-1 gene, while the recitation, "Clusterin" encompasses 3200 known cDNAs and 151 known SNPs of the clusterin gene. Further clusterin and KIM-1 genes are claimed in any animal and thus the skilled artisan would have to determine which of

these thousands of nucleic acids is predictably associated with renal toxicity in any species of animal.

Further the skilled artisan would have to determine if the increased expression of mRNA, protein, or activity of clusterin or KIM-1 is associated with renal toxicity. This would be unpredictable as the specification teaches a single example in which renal toxicity was examined with respect to the mRNA expression of Clusterin and KIM-1. The specification thus does not teach that clusterin of KIM-1 protein or activity are correlated with mRNA expression levels and Greenbaum teaches that protein levels are not predictably correlated with mRNA values. Thus is would be unpredictable to associated protein levels or activities with mRNA levels.

Further the specification does not teach the activity of clusterin or KIM-1 or assays for their activity. Thus one of ordinary skill in the art would be unable to predictably associate an unknown activity or assay with renal toxicity.

Further the skilled artisan would have to determine what level of increased expression of clusterin and KIM-1 mRNA is required to determine renal toxicity. Wu, Cheung, Newton and Greenbuam teach that gene expression is variable across individuals and normalization is critical for predictability. Further Vandesompele teaches that at least 3 controls are required for accurate normalization and thus predictable results. As the specification teaches a single experiment in which normalization is described to a single gene (b-actin experiment 1), it would be unpredictable to associate these results due to the teachings of Vandesompele, Wu, Cheung, Newton and Greenbaum. Further the experiments have not been replicated,

as experiment 2 and 4 merely confirm the expression data with cyclosporine treatment, but do not renal toxicity was examined directly. It would thus making it unpredictable.

The claims requiring specific levels or overexpression or absolute mRNA levels would further be unpredictable, due to the normalization issue described above. Due to the normalization issues one of skill in the art would not be able to adequately determine the fold alteration in expression without knowing the controls by which to normalize expression to and the art clearly teaches the control used is critical. Further the claims drawn to absolute mRNA levels are unpredictable as the specification does not teach these levels or how to obtain these levels and the art teaches that mRNA is variable across species. Further the specification does not teach how to determine absolute mRNA values. Thus it would be unpredictable to use absolute mRNA levels with renal toxicity.

Further it would be unpredictable to associate a specific fold increase in expression of clusterin and KIM-1 with renal toxicity as each experiment appears to teach a different level of increase and only experiment 4 gives the fold expression required in the claims and experiment 4 does not provide that renal toxicity occurs.

Further it would be unpredictable to associate "any" level of cyclosporine treatment with renal toxicity as experiment 4 clearly demonstrates in rats that low doses do not alter gene expression levels while high doses do.

Further it would be unpredictable to extrapolate the data presented in the specification with respect to the effect of cyclosporine A to the cyclosporine, cisplatin, tacrolimus, aminoglycosides, sulfonamides and trimethadione as Perazella teaches

these drugs have different pharmacological action, metabolism, and excretion. Perazella further teaches these compounds affect the kidney differently and thus have different effects. It would thus be unpredictable extrapolate the findings of a single compound to large classes of unrelated compounds without a nexus for extrapolation in the art or specification.

It would be unpredictable to use compounds to modulate gene expression when the specification generally suggests the use of antisense, small molecules, ligands and antaonist, but does not specifically teach which compounds are modulators. Further as Bennett teaches approximately 2% of drug projects result in a drug, thus suggesting the unpredictability of drug design. Robinson further teaches that antisense and RNAi therapeutics have a lot of promise, but many issues to overcome before clinical use. IT would thus be unpredictable to treat with a compound to modulate renal toxicity when the specification does not teach specific samples and the art teaches that drug discovery is unpredictable.

Further it would be unpredictable to associate findings in male rats with female rats as figure 3 clearly depicts that in rats there are differences based on the sex of the animals. Further the specification does not demonstrate that the studies in rats allow for predictable correlations in any other species.

The specification and claims do not adequately describe the normalization controls used such that the skilled artisan would know how to make and use the instant invention, even in the described rat model.

Therefor, in light of the breadth of the claims, the lack of guidance in the specification, the high level of unpredictability in the associated technology, the nature of the invention, the negative teachings in the art, and the quantity of unpredictable experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention as claimed.

10. Claims 1–2, 5-11, 13-14,16-19, 23-28, 31-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejected claims broadly encompass any clusterin or KIM-1 mRNA or protein. The claims do not set forth any structural requirements for clusterin or KIM-1 gene or protein. The claims are further drawn to compounds that modulate renal toxicity, but the claims and specification do not set forth any structural requirements for these compounds.

When the claims are analyzed in light of the specification, the invention encompasses an enormous number of nucleotide molecules. The specification teaches in Table 1 sequences for KIM-1 are available by Genbank accession AF035963, AL159977, AC073225.5, AC025449.6, AF165926, AL449103, AI662116. The specification teaches in Table 1 sequences for clusterin are available by Genbank accession U02391, M64723, M64723, J02908, L00974, M25915, M63379, M64722,

M74816, X14723, AF182509, D14077, L05670, L08235, S70244. The specification does not teach an amino acid sequence of any clusterin or KIM-1 gene.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been disclosed. The instant specification teaches 7 accession numbers for KIM-1 and 15 accession numbers for clusterin. The specification teaches TC1 and TC2, however does not teach the chemical structure of these compounds.

However, Genecard KIM-1 (HAVCR GC05M156389, 11/27/2007, pages 1-9) teaches there are 23 cDNAs and 168 SNPs of the Kim-1 gene. The Clusterin gene card (CLU GCM08M027510, 11/27/2007) teaches there are 3200 known cDNAs and 151 known SNPs of the clusterin gene. Thus the recitation of KIM-1 broadly encompasses 100's of nucleic acids, while clusterin encompasses thousands of nucleic acid molecules.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. other nucleotide sequences or positions with in a specific gene or nucleic acid), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case the specification provides the no structural or functional limitations for clusterin or KIM-1 other than the sequences associated with the accession numbers recited. The claims read in light of the specification and art thus encompass any nucleic acid molecule thousands of nucleic acids and proteins.

The claims do not set forth any structural or functional limitations for modulating compounds. The claims thus broadly encompass any compound that can regulate KIM-1 or clusterin expression by any manner.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acids or compounds regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The current situation is a definition of the compound solely based on its functional utility, as a polymorphism, without any definition of the particular polymorphisms claimed.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words,

structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

In the instant application, the provided information regarding nucleic acid clusterin and KIM-1or modulating compounds, do not constitute an adequate written description of the broad subject matter of the claims, and so one of skill in the art cannot envision the detailed chemical structure of the nucleic acids or compounds encompassed by the claims. Adequate written description requires more than a statement that nucleic acids with a particular quality are part of the invention and reference to a potential method for their identification. The nucleic acid sequence or chemical structure is required.

In conclusion, the limited information provided regarding clusterin and KIM-1 and modulating compounds is not deemed sufficient to reasonably convey to one skilled in the art nucleic acid molecules clusterin and KIM-1 and compounds .

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1–2, 5-11, 13-14,16-19, 23-28, 31-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1–2, 5-11, 13-14,16-19, 23-28, 31-37 recite, " gene expression corresponding to one or more genes." "Corresponding" is not an art recognized term to define the relationship between a gene and gene expression. It is thus unclear is directed to determining the gene expression of KIM-1/clusterin or genes related to or similar to KIM-1/clusterin or genes with similar in function or regulation to the KIM-1 clusterin genes.

Claims 1-2, 5, 9, 10 and 11 recite, "first 10 value lower". It is unclear what is being compared. Appropriate correction is required.

Claim 11 is indefinite it that it recites, "protein corresponding to the gene expression product." "Corresponding" is not an art recognized term to define the relationship between a protein and gene expression product. It is thus unclear is directed to determining the gene expression of KIM-1/clusterin or proteins related to or similar to KIM-1/clusterin or proteins with similar in function or regulation to the KIM-1 clusterin genes.

Claims 2, 5, and 8 are indefinite because the claims do not state how or for what purpose the genes recited are used in steps b and c, it is thus unclear how they further limit the claims. The elected invention is drawn to KIM-1 and clusterin so it is unclear how this phrase is intended to further limit the claim if "are used" is intended to refer to the fact gene expression of these genes was determined.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claim 13 is rejected under 35 U.S.C. 102(b) as being anticipated by Kang et al (American Journal of Physiology Renal Physiology (2001) volume 280, F727-F736).

Claim 13 requires administration of an effective amount of a modulating compound that modulates the synthesis, expression or activity or one of the recited genes or gene expression products, so that at least one symptom of renal toxicity is ameliorated. The claim does not require detection of the gene or gene expression product.

Kang et al treatment of Sprague-Dawly rats with cyclosporine A (CsA) (see page F728, 2nd column, experimental protocol). Kang teaches a control group was treated with PBS and the other was treated with VEGF (see page F728, 2nd column, experimental protocol). Kang et al teaches the VEGF treatment resulted in lower blood pressure, osteopontin expression, macrophage infilitration, collagen 3 deposition and stimulated resolution of arteriolopathology. Thus Kang teaches treatment of an individual with a modulating compound, that alters the expression or activity of clusterin or KIM-1, so as to ameliorate at least one symptom of renal toxicity.

Summary

No claims are allowed.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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